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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,008	DE HAEN, CHRISTOPH	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are currently pending and under consideration.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

It is noted that examiner has established a priority date of 11/13/2003 for the instant application, 10/535,008 because the priority of the instantly claimed invention is based on the Italian application MI3002A 002411 cited above, which have not been translated and the Examiner is unable to determine the information in the document. If applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, 11/13/2003 for the instantly claimed application serial number 10/535,008, applicant is invited to submit a proper translation of the priority document and to point to page and line where support can be found establishing an earlier priority date. If Applicants choose to file a translation, then the translation must be filed together with a statement that the translation of the certified copy is accurate, see MPEP 201.15.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bispecific antibody for the diagnosis or treatment of gastric tumors that recognizes E-cadherin with an in-frame deletion in exon 8 and E-cadherin

with an in-frame deletion in exon-9 conjugated to at least one unit which supplies a diagnostic signal or therapeutic effect, does not reasonably provide enablement for an agent for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, said agent comprising: a. a recognition unit consisting of a conjugate of m recognition molecules, where m is at least 2 and equal or smaller than n, and each recognition molecule is specific for a different altered form of the protein, and, b. at least one unit which supplies a diagnostic signal or therapeutic effect, conjugated with or included in said specific recognition unit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to an agent for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, said agent comprising: a. a recognition unit consisting of a conjugate of m recognition molecules, where m is at least 2 and equal or smaller than n, and each recognition molecule is specific for a different altered form of the protein, and, b. at least one unit which supplies a diagnostic signal or therapeutic effect, conjugated with or included in said specific recognition unit.

When given the broadest reasonable interpretation the claims are drawn to an unlimited number of agents with an unlimited number of binding specificities that are for the diagnosis or treatment of any tumor. Additionally, the construction of part 1b is such that the unit which supplies diagnostic or therapeutic effect is not required to be bound to the recognition unit of 1a, thus the claims include agents that are mixtures of the agents in 1a and 1b.

The specification teaches that one of the most frequently studied families of altered proteins exposed on the surface of tumour cells derives from E-cadherin, a calcium-dependent cell adhesion molecule firmly anchored in the cytoplasmic membrane. More than 33 distinct somatically mutated forms of E-cadherin have been identified in infiltrative lobular breast cancer. Most of these mutated forms are truncated proteins resulting from out of frame deletion mutations. Normally tumors in each patient only display one particular mutated form of E-cadherin, see page 1.

The specification teaches that human gastric tumours of the diffuse type have been described to frequently express somatically mutated E-cadherins. In this tumour, besides point mutations leading to the replacement of single amino acids, the mutations often involve an exon-skipping in-frame deletion, leading to a minimally shortened and regionally altered amino acid sequence. Such in-frame deletions have been observed in correspondence of at least 9 of the 16 exons in the E-cadherin gene. Deletions at exon 8 or 9 are by far the most frequent, followed by deletions at exon 10 and 7. These mutations are specific for tumour cells, and are never present in healthy cells; they consequently constitute an ideal target for immunotherapeutic approaches. Identification of the particular type of mutated E-cadherin present in the tumours of a patient, requires corresponding immunodiagnostic approaches, see pages 1-2.

The specification presents what appear to be hypothetical examples of bispecific antibodies for mutated exon 8 and mutated exon 9 of E-cadherin and a toxin. The specification speculates that this antibody will be useful for the treatment and diagnosis of stomach carcinomas, see Examples 12 and 13.

At the time the invention was made, monoclonal antibodies to the in-frame deletion of exon 8 and 9 mutant of E-cadherin were known and were shown to be useful for the treatment of gastric cancer, see Senekowitsch-Schmidtke et al. (Cancer Res. April 1, 2001, 61:2804-2808, IDS), Huber et al. (Clin. Can. Res. Sep. 1, 2003, 9:3922s-3928s, IDS), Becker et al. (US Patent No. 6,447,776, 09/10/02, IDS), and Höfler et al. (US Patent No. 6,723,320, 4/20/2004).

However, one cannot extrapolate the teachings of the specification and the prior art of record to enable the scope of the claims because a nexus has not been established for the broadly claimed agent and the diagnosis and treatment of any tumor.

Firstly, one of skill in the art would not expect that one could predictably make the myriad of agents encompassed by the claims with a multitude of binding specificities. The instant claims are broadly drawn to include binding agents which bind to altered forms of a protein or glycoprotein, said altered protein or glycoprotein being present as "the number n, smaller than N, or N different altered forms" present in a tumor cell population. It is noted that the numbers n and N do not have an upper limit, and have a lower limit defined only by "m is at least 2 and equal to or smaller than n" Thus is can be concluded that ***n*** is at least 2, and therefore ***N*** is at least 3 in order for n to be smaller than ***N***. When given the broadest reasonable interpretation, the term "binding agent" includes antibodies, polypeptides, polysaccharides as well as inorganic and organic molecules that are characterized only as binding to an altered form of a protein or glycoprotein which meets the numerical limitations of claim 1 with respect to the number of altered forms of a genus of glycoproteins on any tumor type. Thus, the claims are drawn to a multitude of unknown, undefined, and uncharacterized agents, beyond those binding agents which are antibodies, that bind to a myriad of unknown and undefined proteins, one of skill in the art would could not predictably make and use the broadly claimed agents for the diagnosis and treatment of the broadly claimed tumor commensurate with the scope of the claims, other than bispecific antibodies that recognizes an E-cadherin with an in-frame deletion in exon 8 and E-cadherin with an in-frame deletion in exon-9, without undue experimentation.

The specification fails to teach how to make other binding agents, such as polysaccharides, non-peptide organic molecules and inorganic molecules which comprise recognition units which discern between an altered form of a glycoprotein or altered form or a protein. At the time the application was filed, it was well known in the art how to carry out

subtractive immunization, or how to immunize mice with peptides comprising unique epitopes (Rao, FASEB Journal, 2001, Vol. 15, page A879) in order to isolate polyclonal antibodies which recognized said unique epitope. However, an altered form of a protein or glycoprotein can be a protein or glycoprotein differing by as little as one amino acid. The specification fails to teach how to make non-antibody-based binding agents which can selectively bind to the altered form of the glyoprotein or protein, and clearly fails to teach how to make altered forms of the glycoprotein or protein which differ by a small alteration, such as a single amino acid.

Furthermore, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Kaiser (Science, 2006, 313: 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been

an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). In addition, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the agent. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The agent may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the agent. In addition, the agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate model system, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the broadly claimed agents would be effective for the treatment of the broadly claimed tumor based on the speculative examples taught in the specification. Additionally, although the art teaches that antibodies to the exon 9 E-cadherin mutants coupled to a radioactive isotope were effective for the treatment of gastric tumors (see Huber et al. Fig. 1), no data in the specification nor art of record is provided that would suggest that the broadly claimed agent or

even antibodies to the exon 8 or 9 E-cadherin mutants would be effective for treatment when a therapeutic agent is not conjugated to the recognition molecule.

Furthermore, one of skill in the art would not predictably expect that any agent to be useful for the diagnosis and treatment of all tumors as tumors are well known in the art to be heterogeneous in nature and all tumors do not predictably express the broadly claimed protein targets. In particular cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, cancers that originate from different tissue types would have different structures as well as etiologies and would present differently. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Additionally, Senekowitsch-Schmidtke et

al. (Cancer Res. April 1, 2001, 61:2804-2808, IDS) teach that the in-frame E-cadherin deletion mutants of exon 8 and 9 are only characteristic of gastric carcinomas, see p. 2804, 1st col. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between antibodies to E-cadherin in-frame deletion mutants of exon 8 and 9 and the diagnosis and treatment of gastric cancer to the broadly claimed agent and diagnosis and treatment of the broadly claimed tumors, based on the information in the specification and known in the art without undue experimentation.

Furthermore, as drawn to the fragments of immunoglobulins in claim 2, the teaching of the specification cannot be reasonably extrapolated to enable the scope of the claims because one of skill in the art could not predict that any fragment of an immunoglobulin would be useful in diagnosing or treating tumors. Fragments of antibodies include not only the antigen-binding region but also the Fc portion Janeway et al. (Immunobiology 5, 2001, Fig. 3-1 and 3-3). One of skill in the art would expect that only antigen-binding fragments of the immunoglobulin would be useful in diagnosing or treating tumors. Thus, one of skill in the art could not predict that the invention would function as claimed. Therefore, practice of the invention would require undue experimentation

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and

the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given the lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

4. Claims 1-21 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to an agent for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, said agent comprising: a. a recognition unit consisting of a conjugate of m recognition molecules, where m is at least 2 and equal or smaller than n, and each

recognition molecule is specific for a different altered form of the protein, and, b. at least one unit which supplies a diagnostic signal or therapeutic effect, conjugated with or included in said specific recognition unit. The claims lack any limitation on said agent and thus are drawn to a genus of agents for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue. When given the broadest reasonable interpretation, the term "an agent for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue" encompasses any type of compound, protein or non-protein such as a small organic molecule, a carbohydrate or polysaccharide, that can bind to a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, therefore the genus of binding agents is highly variant encompassing compounds which vary significantly both in structure and function from each other. The description of a bispecific antibody to exon 8/ exon 9 E-cadherin deletion mutants fails to adequately describe the genus of agents because said genus tolerates members which differ significantly in both structure and function from said bispecific antibody. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of "an agent for the diagnosis or treatment of those tumours that in an

individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, said agent comprising: a. a recognition unit consisting of a conjugate of m recognition molecules, where m is at least 2 and equal or smaller than n, and each recognition molecule is specific for a different altered form of the protein, and, b. at least one unit which supplies a diagnostic signal or therapeutic effect, conjugated with or included in said specific recognition unit" at the time the invention was filed.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the

identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date antibodies to the E-cadherin exon 8 and 9 deletion mutants were known in the art (for example, U see Senekowitsch-Schmidtke et al. (Cancer Res. April 1, 2001, 61:2804-2808, IDS), Huber et al. (Clin. Can. Res. Sep. 1, 2003, 9:3922s-3928s, IDS), Becker et al. (US Patent No. 6,447,776, 09/10/02, IDS) , and Hofler et al. (US Patent No. 6,723,320, 4/20/2004), however, these few antibodies fail to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the few known art known antibodies, and including binding agents which are polysaccharides, polypeptides, non-peptide organic molecules and inorganic molecules.

In the instant case the genus is only described as a definition by function (i.e. binding to altered forms or glycoproteins or altered forms of proteins), and beyond the speculative example of a bispecific antibody to E-cadherin deletion mutants, one of skill in the art cannot readily visualize or recognize the identity of members of the genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-8, 12, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Luber et al. (US Patent App. Pub. 2006/0002934, May 15, 2002) as evidenced by Janeway et al. (Immunobiology 5, 2001, Fig. 3-1 and 3-3) and Hakai (Nature Cell Biol. March, 2002, 4:222-231, S1-S2).

1. An agent for the diagnosis or treatment of those tumours that in an individual patient expose on the cell surface only a number n smaller than N of N different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients, said altered forms of the protein deriving from alterations of a normal form present in healthy tissue, said agent comprising: a. a recognition unit consisting of a conjugate of m recognition molecules, where m is at least 2 and equal or smaller than n, and each recognition molecule is specific for a different altered form of the protein, and, b. at least one unit which supplies a diagnostic signal or therapeutic effect, conjugated with or included in said specific recognition unit.

2. An agent as claimed in claim 1, wherein the recognition molecules are selected from among immunoglobulins or fragments thereof, polypeptides and polysaccharides.

3. An agent as claimed in claim 2, wherein at least one recognition molecules is an Fab, F(ab') or scFv fragments.

4. An agent as claimed in claim 2, wherein the recognition molecules are conjugated to one another by means of a direct covalent bond or by means of a multipurpose linker able to form covalent bonds with the molecules, and/or as a result of the expression of fused genes with suitable linker regions.

5. An agent as claimed in claim 1, wherein at least one of the specific recognition molecules recognizes a protein altered as a result of one or more mutations.

6. An agent as claimed in claim 1, wherein at least one of the specific recognition molecules recognises a protein altered as a result of post-translational modifications, deficient post-translational modifications, absence of post-translational modifications or partial degradation.

7. An agent as claimed in claim 1, wherein one of the specific recognition molecules recognizes an E-cadherin with a deletion in exon 8 and another molecule recognises E-cadherin with a deletion in exon 9.

8. An agent as claimed in claim 1, wherein the unit able to provide a diagnostic signal or therapeutic effect is linked directly, via an avidin/biotin or streptavidin/biotin system or via a suitable covalent linker to one of the recognition molecules of the recognition unit, or to the linker that holds the recognition molecules together.

12. An agent as claimed in claim 1, wherein the unit able to provide a diagnostic signal or therapeutic effect is a radioactive halogen, a chelate of an radioactive isotope, a chelate of a paramagnetic metal ion, a stabilized particle of iron oxide, a stabilized microbubble, a fluorescent, phosphorescent or near-infrared radiation-absorbing compound, a cytotoxic compound, a natural or synthetic toxin, or a photodynamic compound able to generate reduced oxygen species or singlet oxygen by irradiation.

18. An agent as claimed in claim 1, wherein the various recognition molecules are conjugated to one another, or said recognition molecules are conjugated with the therapeutic or diagnostic unit, by reaction between sulfhydryl-reactive groups and the sulfhydryl groups present, or generated by reduction of disulfide bridges, on said units/molecules.

19. Pharmaceutical or diagnostic compositions containing an agent as claimed in claim in admixture with a suitable vehicle.

Luber et al. teach bispecific antibodies directed against del 8 and del 9 mutants of E-cadherin coupled to toxins for the treatment of gastric cancer in pharmaceutical compositions, para 0013, 0028-0036, and the claims. One of skill in the art would immediately envision making the pharmaceutical composition with a suitable vehicle such as buffered saline. Additionally, antibodies are well known in the art to comprise Fab fragments and are together joined by di-sulfide bonds, see Janeway et al. Fig. 3-1 and 3-3.

Although the reference does not specifically state that the antibodies recognize a protein altered as a result of post-translational modifications, deficient post-translational modifications, absence of post-translational modifications or partial degradation, given that Hakai et al. teach that E-cadherin is post-translationally modified by phosphorylation and ubiquitination, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 9-11, 13-17, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Luber et al. (US Patent App. Pub. 2006/0002934, May 15, 2002) as applied to claims 1-8, 12 and 19 above, in view of Rosen et al (US 2002/0042386, April 11, 2002), further in view of Alvarez et al. (US Patent No. 4,741,900, May 3 ,1988), further in view of Uggeri et al. (US Paent No. 5,660,814, Aug. 26,1997) and in view of Stratagene Catalog 1988, p. 39.

The claims are drawn to:

9. An agent as claimed in claim 8, wherein the unit able to provide a diagnostic signal or therapeutic effect is conjugated covalently with biotin, and the recognition unit is conjugated covalently with avidin or streptavidin.

10. An agent as claimed in claim 8, wherein the unit able to provide a diagnostic signal or therapeutic effect is conjugated covalently with avidin or streptavidin, and the recognition unit is conjugated covalently with biotin.

11. An agent as claimed in claim 1, wherein the unit able to provide a diagnostic signal or

therapeutic effect is part of the bond between the recognition molecules of the recognition unit.

13. An agent as claimed in claim 12, wherein the radioactive halogen is selected from 123I, 124I, 125I, 131I, 75Br, 76Br, 77Br and 82Br.

14. An agent as claimed in claim 12, wherein the radioactive isotope is selected from among 99mTc, . 111In, 203Pb, 66Ga, 67Ga, 68Ga, 161Tb, 72As, 113mIn, 97Ru, 62Cu, 64Cu,.67Cu, 52Fe, 52mMn, 51Cr, 186Re, 188Re, 77As, 90Y, 169Er, 121Sn127Te, 143Pr, . 198Au, 199Au, 109Pd, 165Dy, 149Pm, 151Pm, .153Sm, 157Gd, 159Gd, 166Ho,.172Tm,169Yb, 175Yb, 177Lu, 105Rh, 111Ag47Sc, 140La, 211At, 212Bi, 213Bi, 212Pb, 225 Ac, 223Ra, 224Ra and 227Th.

15. An agent as claimed in claim 12, wherein the paramagnetic metal is selected from the metal elements having an atomic number of 21-29, 39, 42, 44, 49 or 57-83.

16. An agent as claimed in claim 15, wherein the metal is selected from among Gd3+, Fe3+, Eu3+, Dy3+, La3+, Yb3+ and Mn.2+.

17. An agent as claimed in claim 15, wherein the metal or isotope is chelated by chelating groups deriving from diethylenetriamine or from polyamine macrocycles, both substituted by residues bearing carboxy, phosphonic or sulphonic groups.

20. Compositions as claimed in claim 19, in the form of a kit containing: a. the unit able to provide a diagnostic signal or therapeutic effect, covalently conjugated with biotin, and b. a recognition unit covalently conjugated with avidin or streptavidin.

21. Compositions as claimed in claim 19, in the form of a kit containing: a. the unit able to provide a diagnostic signal or therapeutic effect covalently conjugated with avidin or streptavidin, and b. a recognition unit covalently conjugated with biotin

Rosen teaches that mutant E-cadherin is thought to be involved with progression of epithelial tumors, see para, 0016. Rosen et al. contemplate bispecific, trispecific, or multipsecific, for the diagnosis and treatment of cancer, recombinantly or covalently fused to radionuclides or toxins in pharmaceutically acceptable compositions, see para. 0228- 238, 0282, 0299,0300, 0341,and 0342. Rosen et al. contemplates antibodies recombinantly fused or chemically conjugated with linker sequences through covalent attachments, see para. 0225, 0238, 0277, and 0281. Rosen et al. contemplates streptavidin/biotin and avidin/biotin coupling of detectable labels directly or indirectly through linkers to the antibodies of the invention, see 0281. Rosen et al. contemplate coupling the antibodies of the inventions to biotin, see 0342. Rosen et al. contemplate coupling the antibodies of the invention to paramagnetic metal ions, fluorescent materials and 125I, 131I, 111In or 99Tc and other toxins, see para. 0281-0282. Rosen et al. contemplate attaching metals to antibodies using diethylenetriaminepentacetic or macrocylic chelators acid for the attachment of metal ions to proteins and antibodies, see 0260 and 0428. Rosen et al. contemplate kits comprising labeled antibodies of the invention, see para. 0350-0356.

Alvarez et al. teach methods of coupling metal ions to antibodies for radiological imaging using DTPA, see col. 2-5. Alvarez et al. teach coupling the paramagnetic metal ions ^{57}Iron and ^{58}Iron to the antibody, see col. 15. Alvarez et al. teach attaching chelated metal ions to reduced sulfhydryls that normally link the antibodies heavy chain to form a covalent bond that does not interfere with the antigen binding site of the immunoglobulin, see col. 13.

Uggeri et al. teach Metal ions of atomic number between 20-31, 39, 42, 43, 44, 49 or between 57 and 83; particularly preferred are Fe(2+), Fe(3+), Gd(3+), Eu(3+), Dy 3+), La(3+),

Yb (3+) or Mn(2+) for coupling to antibodies and other biological molecules for diagnostic imaging, see, Abstract, col. 1 and col.6.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would be *prime facie* obvious to one of skill in the art at the time the invention was made to link the diagnostic and recognition units of the agent with biotin and streptavidin/avidin covalently wherein the diagnostic and recognition units are alternatively linked to biotin or streptavidin/avidin as Rosen et al. teach theses molecules for coupling of antibodies to detectable agents using biotin or streptavidin/avidin and the use of these agents was well established in the art at the time was made. It would be obvious to alternatively link biotin or streptavidin/avidin to the diagnostic and recognition units as these are the only alternatives available for using these linking agents.

It would *prime facie* be obvious to link the diagnostic metal ion to the sulfhydral groups of the antibodies that normally link the heavy chains and link the two recognition units because Alvarez teaches that the chelated metal ions can be attached here without disruption of the antigen binding site and this is where the two Fab fragments are naturally linked at this point. Thus one of skill in the art would have been motivated with a reasonable expectation of success to link the recognition molecules together by disulfide bonds to chelated metal ions.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the bispecific antibodies conjugates into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus

one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Thus, one of skill in the art would have been motivated with a reasonable expectation of success to make bispecific antibodies to the E-cadherin exon 8 and 9 in-frame deletion mutants conjugated to diagnostic or therapeutic agents in a kit as claimed with a reasonable expectation of success.

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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